ESIM Annual Lectures 2023

8th Annual Internal Medicine Conference and Health Exhibition

Theme:
Harmonizing Medical Education with Clinical Services to Improve Healthcare Quality in Ethiopia: Opportunities, Challenges and the Way Forward

Inter Luxury Hotel | Addis Ababa, Ethiopia
Perioperative HsTroponinT
use in
Non-cardiac Patients

Shibikom Tamirat, Assistant Prof
Adult and Pediatric Cardiac Surgeon
General Surgeon
Disclosure

Conflicts of Interest

Roche
Timeline of the development of cardiac biomarkers for the diagnosis of acute myocardial infarction
Introduction

• Troponin complex regulates the contraction of striated muscles and consists of three subunits
  • Troponin C
  • Troponin T
  • Troponin I
Human Cardiac Troponin Core Complex

- Blue = troponin C
- Green = troponin I
- Magenta = troponin T.
• Troponin T and troponin I are present in cardiac and skeletal muscles, but are encoded by different genes

• Amino acid sequence of cardiac troponin C and skeletal troponin C is identical
  • No such assays have been developed for the troponin C component.
Introduction

- Troponin T levels exceeding the 99th percentile of a normal reference population are designated as the decision level for the diagnosis of an MI in conjunction with that patient’s clinical presentation.
- High-sensitivity assays allows for lower levels of cardiac troponins to be assessed for other etiologies.
  - Even minimal increases of troponin levels are associated with unfavorable cardiovascular and all-cause mortality outcomes.
  - This association is also independent of conventional risk factors.
Troponin elevation following cardiac cell necrosis starts within 2–3 hours
Peaks in approximately 24 hours
Persists for 1–2 weeks.
• There are a number of cTnI assays on the market.
  • These cTnI assays are not standardized and studies have documented substantial differences across methods
• In contrast to cTnI, there is only one manufacturer for the cTnT assay and the above shortcomings could be avoided
What makes Roche special??????

Due to patent regulations, a single manufacturer (Roche Diagnostics) distributes cTnT.
## RELATIVE RISK

<table>
<thead>
<tr>
<th>hs-TnT (ng/L)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;6</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Moderate</td>
<td>6-22</td>
<td>6-14</td>
</tr>
<tr>
<td>High</td>
<td>&gt;22</td>
<td>&gt;14</td>
</tr>
</tbody>
</table>
Non-Cardiac Surgery

- 200 million non-cardiac surgeries are performed each year
  - 10 million of these surgeries have overt cardiovascular complications, including short-term mortality
Overt Cardiovascular Complications
Perioperative myocardial injury (PMI) was defined as an elevation of \( \text{hsTnT} > 14 \text{ ng/L (99th percentile)} \) without consideration of a preoperative level.

Among 21,842 patients ≥45 years of age undergoing noncardiac surgery at 23 centers worldwide, nearly 1 in 5 had evidence of myocardial injury as determined by elevated high-sensitivity troponin T (hsTnT) in the first 3 days postoperatively, 93% without any ischemic symptoms to support a diagnosis of myocardial infarction.

There was no specific protocol for response to elevated levels, and hsTnT was not obtained preoperatively in all study participants.

PMI occurs in 18%.

There was a graded increase in 30-day mortality with higher hsTnT levels.

JAMA. 2017;317(16):1642-1651
Puelacher cohort

- PMI required an absolute hsTnT increase of ≥14 ng/L above the preoperative level in ≤48 hours postoperatively
- They examined PMI among 2018 consecutive patients at increased risk for cardiovascular complications (≥65 years of age or ≥45 years of age with a history of coronary artery dis-ease, peripheral artery disease, or stroke) who underwent 2546 non-cardiac surgeries at a single hospital.
- HsTnT was assessed both pre- and postoperatively as part of a standard-of-care protocol that included specific assessments and an automatic trigger for cardiology consultation for patients with PMI.
- PMI occurs in 16% of all surgeries

Circulation. 2018;137:00–00. DOI: 10.1161/CIRCULATIONAHA.117.030114
• PMI was associated with nearly 3-fold higher adjusted 30-day mortality risk and 1.6-fold higher 1-year mortality risk

• Similar to VISION, most cases of PMI were clinically silent: only 6% had typical anginal chest pain, only 18% had any symptoms of ischemia, and only 29% met any criteria for spontaneous myocardial infarction.

• 30-day mortality was similar among cases of PMI with and without symptoms and regardless of whether any criteria for spontaneous myocardial infarction were met.
Meta-analysis of preoperative high-sensitivity cardiac troponin measurement in non-cardiac surgical patients at risk of cardiovascular complications

2020 BJS Society Ltd BJS 2020; 107: e81–e90 Published by John Wiley & Sons Ltd
<table>
<thead>
<tr>
<th>Reference</th>
<th>Assay type</th>
<th>Cut-off (ng/l)</th>
<th>Preoperative hs-cTn raised</th>
<th>Preoperative hs-cTn not raised</th>
<th>Weight (%)</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcock et al.</td>
<td>hs-cTnT</td>
<td>14</td>
<td>30 of 109</td>
<td>49 of 243</td>
<td>15:26</td>
<td>1.38 (0.92, 2.02)</td>
</tr>
<tr>
<td>Nagole et al.</td>
<td>hs-cTnT</td>
<td>14</td>
<td>54 of 247</td>
<td>28 of 361</td>
<td>14:89</td>
<td>2.82 (1.84, 4.32)</td>
</tr>
<tr>
<td>Weber et al.</td>
<td>hs-cTnT</td>
<td>14</td>
<td>22 of 233</td>
<td>14 of 746</td>
<td>12:14</td>
<td>5.03 (2.62, 9.67)</td>
</tr>
<tr>
<td>Gillmann et al.</td>
<td>hs-cTnT</td>
<td>17:8</td>
<td>28 of 119</td>
<td>13 of 336</td>
<td>12:50</td>
<td>6.08 (3.26, 11.35)</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>hs-cTnT</td>
<td>6:5</td>
<td>44 of 107</td>
<td>17 of 155</td>
<td>13:98</td>
<td>3.75 (2.27, 6.20)</td>
</tr>
<tr>
<td>Puelacher et al.</td>
<td>hs-cTnT</td>
<td>14</td>
<td>206 of 931</td>
<td>63 of 1006</td>
<td>16:58</td>
<td>3.53 (2.70, 4.62)</td>
</tr>
<tr>
<td>Gualandro et al.</td>
<td>hs-cTnT</td>
<td>14</td>
<td>25 of 87</td>
<td>32 of 156</td>
<td>14:66</td>
<td>1.46 (0.93, 2.28)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>410 of 1833</td>
<td>216 of 3003</td>
<td>100:00</td>
<td>2.92 (1.96, 4.37)</td>
</tr>
</tbody>
</table>

Heterogeneity: $t^2 = 0.23; \chi^2 = 34.56, 6$ d.f., $P < 0.001$; $I^2 = 82.6\%$

Test for overall effect: $Z = 5.24$, $P < 0.001$
### Short-term mortality

<table>
<thead>
<tr>
<th>Reference</th>
<th>Assay type</th>
<th>Cut-off (ng/l)</th>
<th>Preoperative hs-cTn raised</th>
<th>Preoperative hs-cTn not raised</th>
<th>Weight (%)</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weber et al.²³</td>
<td>hs-cTnT</td>
<td>14</td>
<td>16 of 233</td>
<td>9 of 746</td>
<td>41.63</td>
<td>5.96 (2.55, 12.71)</td>
<td></td>
</tr>
<tr>
<td>Puelacher et al.¹⁹</td>
<td>hs-cTnT</td>
<td>14</td>
<td>44 of 931</td>
<td>9 of 1006</td>
<td>53.07</td>
<td>5.26 (2.59, 10.76)</td>
<td></td>
</tr>
<tr>
<td>Kim et al.²⁰</td>
<td>hs-cTnl</td>
<td>6.5</td>
<td>3 of 107</td>
<td>1 of 155</td>
<td>5.31</td>
<td>4.35 (0.46, 41.22)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>63 of 1271</td>
<td>19 of 1907</td>
<td>100.00</td>
<td>5.39 (3.21, 9.06)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.00; \chi^2 = 0.06$, 2 d.f., $P = 0.972; I^2 = 0.0\%$

Test for overall effect: $Z = 6.37, P < 0.001$
### Long-term mortality

<table>
<thead>
<tr>
<th>Reference</th>
<th>Assay type</th>
<th>Cut-off (ng/l)</th>
<th>Preoperative hs-cTnT raised</th>
<th>Preoperative hs-cTnT not raised</th>
<th>Weight (%)</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagele et al.</td>
<td>hs-cTnT</td>
<td>14</td>
<td>62 of 247</td>
<td>40 of 361</td>
<td>47.43</td>
<td>2.27 (1.58, 3.26)</td>
<td>-</td>
</tr>
<tr>
<td>Puelacher et al.</td>
<td>hs-cTnT</td>
<td>14</td>
<td>174 of 931</td>
<td>52 of 1006</td>
<td>52.57</td>
<td>3.62 (2.69, 4.86)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>236 of 1178</td>
<td>92 of 1367</td>
<td>100.00</td>
<td>2.90 (1.83, 4.59)</td>
<td>-</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.08; \chi^2 = 3.88, 1\text{ d.f.}, P = 0.049; I^2 = 74.2\%$

Test for overall effect: $Z = 4.52, P < 0.001$
Way forward???
Large randomized clinical trials would be needed to confirm clinical benefit of medical interventions based on routine hsTnT screening postoperatively.

But they seem warranted:

- Given the scope of the problem and
- Potential to impact outcome if treatment benefit was found.

In the meantime, medical treatment is generally safe and would seem to have few downsides.
• A bigger challenge will be determining which patients diagnosed with PMI should undergo additional noninvasive or invasive cardiac testing.

• Indiscriminately adding stress testing or coronary angiography to the management of 1 in 5 of the 200 million patients undergoing non-cardiac surgery worldwide would be resource-intensive.

• It is not clear whether the potential benefits would outweigh the risks or expense of testing.
MANAGING HYPERTENSION FOR OUTCOMES; What is the Ideal pathway?

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Assistant Professor of Medicine
Consultant Internist and Cardiologist
August 2023

Ethiopian Society of Internal Medicine(ESIM): Annual event
Outline of Presentation

• Definition and Epidemiology
• Benefits of Blood pressure reduction
• When to initiate and to what target?
• Beyond Blood pressure reduction
  – Which pharmacologic agent?
  – Single pharmacologic agent or combination?
• Local evidences for African patients
• ESH 2023 Guideline update
### Definitions of Hypertension According to Office, Ambulatory, and Home Blood Pressure Levels

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Office BP</strong>*</td>
<td>≥ 140</td>
<td>and/or ≥ 90</td>
</tr>
<tr>
<td><strong>Ambulatory BP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime (or awake), mean</td>
<td>≥ 135</td>
<td>and/or ≥ 85</td>
</tr>
<tr>
<td>Nighttime (or asleep), mean</td>
<td>≥ 120</td>
<td>and/or ≥ 70</td>
</tr>
<tr>
<td>24 hour, mean</td>
<td>≥ 130</td>
<td>and/or ≥ 80</td>
</tr>
<tr>
<td><strong>Home BP, mean</strong></td>
<td>≥ 135</td>
<td>and/or ≥ 85</td>
</tr>
</tbody>
</table>

*Refers to conventional office BP rather than unattended office BP.

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure. Adapted from Williams B, et al. *J Hypertens* 2018;36(12):2284-309.
## Classification of Hypertension

**FIGURE 3**

<table>
<thead>
<tr>
<th>SBP [mmHg]</th>
<th>DBP [mmHg]</th>
<th>ESHT/ESC 2018</th>
<th>AHA/AACC 2017</th>
<th>Position of the DHL, 2017</th>
<th>NICE 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120 and &lt;80</td>
<td>Optimal</td>
<td>Normal</td>
<td>Optimal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>120–129 and &lt;80</td>
<td>Normal</td>
<td>Elevated</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>130–139 or 80–89</td>
<td>Upper range of normal</td>
<td>Grade I hypertension</td>
<td>Upper range of normal</td>
<td>Upper range of normal</td>
<td>Upper range of normal</td>
</tr>
<tr>
<td>140–159 or 90–99</td>
<td>Grade I hypertension</td>
<td>Grade II hypertension</td>
<td>Grade I hypertension</td>
<td>Grade I hypertension (≥135/85 mmHg)*</td>
<td>Grade I hypertension</td>
</tr>
<tr>
<td>160–179 or 100–109</td>
<td>Grade II hypertension</td>
<td>Grade II hypertension</td>
<td>Grade II hypertension</td>
<td>Grade II hypertension (≥150/95 mmHg)*</td>
<td>Grade II hypertension</td>
</tr>
<tr>
<td>≥ 180 or ≥ 110</td>
<td>Grade III hypertension</td>
<td>Grade II hypertension</td>
<td>Grade III hypertension</td>
<td>Severe hypertension</td>
<td>Severe hypertension</td>
</tr>
</tbody>
</table>

A comparison of the new definitions of normal blood pressure and the different grades of high blood pressure by the American Heart Association (AHA) and American College of Cardiology (ACC) with the definitions by the European Society of Cardiology (ESC) and European Society of Hypertension (ESH), as well as the most recent position of the German Hypertension League (Deutsche Hochdruckliga, DHL) and the National Institute for Health and Care Excellence (NICE) of the United Kingdom.

The lowering of cutoff values led to an increase in the prevalence of hypertension in the USA from 32% to 46%.

*The value refers to further measurements in the outpatient setting or at home.

DBP, diastolic blood pressure. SBP, systolic blood pressure.
Hypertension is the leading cause of death worldwide\textsuperscript{1}

Deaths attributable to individual risk factors

- High blood pressure
- Smoking and secondhand smoke
- Diets low in fruits
- High BMI
- High blood glucose
- Physical inactivity and low physical activity
- High dietary salt
- Alcohol use
- Diets low in nuts and seeds
- High serum cholesterol
- Diets low in vegetables
- Diets low in whole grains
- Diets low in fish and seafood

10.4 million deaths each year\textsuperscript{2}

Risk Factors For Global Burden of Disease and Mortality

Hypertension - Global burden

_Lancet_ 2021;398:957-80

- Global prevalence in 2019: ~ 1.3 billion [people aged 30-79 years]
  - > 1 billion (82%) in low- & middle- income countries

- Global age-standardized prevalence: 34% ♂ & 32% ♀

- Global Rx/control rate: 38%/18% ♂ & 47%/23% ♀

- SSA: 60-70% ♂ & 50-60% ♀ with HTN not diagnosed; control rates 9% ♂ & 13% ♀

- Estimated to affect 1/3 of the world’s population by 2025
Hypertension burden - Ethiopia

Percentage of respondents with raised blood pressure, or currently taking medication for raised blood pressure, by sex, Ethiopia NCD STEPS, 2015

Risk factor Prevalence in Ethiopia and trends

PLOS ONE 2021 data

Prevalence and risk factors of hypertension among adults: A community based study in Addis Ababa, Ethiopia

Merenet Hailu Assefa ¹, Azaweye Worku Yared², Negussie Deyesse Kabeta³, Desale Woldemariam²

¹ School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia; ² College of Health Science, Addis Ababa University, Addis Ababa, Ethiopia

Results

In this study, a total of 3560 participants were included. The median age was 32 years (IQR 25, 45). More than half (57.3%) of the respondents were females. Almost all (96.2%) of participants consumed vegetables and or fruits less than five times per day. Eight hundred and sixty-five (24.3%) of respondents were overweight, while 287 (8.1%) were obese. One thousand forty-nine (29.24%) of respondents (95% CI: 27.75-30.74) were hypertensive, of whom two-thirds (61.95%) did not know that they had hypertension.
Hypertension burden - Ethiopia

- 38 studies; 51,427 participants

- Overall prevalence: 21.8%
  - ♂: 23.2%
  - ♀: 19.6%

- Highest prevalence: Addis Ababa 25.4%

- Lowest prevalence: Tigray 15.4%

2023 ESH Guidelines for the management of arterial hypertension

NEW updates FOR management of hypertensive patients!!!!!

Patient Evaluation

- History
- P/E
- Pertinent investigations
  - Risk stratification on the basis of findings
  - Should start from appropriate measurement of BP!
Treatment
Benefits of Blood Pressure Reduction


BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease.


Each reduction in BP of 10 mmHg leads to vascular risk reductions.

- Reduction in endpoint for each 10 mmHg reduction in office BP, %
  - CVD events: -20% (95% CI, 0.77 to 0.83)
  - CHD: -17% (95% CI, 0.78 to 0.88)
  - Stroke: -27% (95% CI, 0.68 to 0.77)
  - Heart failure: -28% (95% CI, 0.67 to 0.78)
  - All-cause mortality: -13% (95% CI, 0.84 to 0.91)
Hypertension Is Not Adequately Controlled

> 50% of adults with raised BP were not diagnosed with hypertension

< 30% of adults on medication had blood pressure controlled

BP, blood pressure; DHS, Demographic and Health Survey; STEPS, WHO STEPwise approach to surveillance.
2023 ESH Guidelines for the management of arterial hypertension

Grade 1 Hypertension
BP 140–159/90–99
Asymptomatic, without HMOD and CVD
At least 1 additional office visit (e.g. within 4 weeks)

Grade 2 Hypertension
BP 160–179/100–109
Symptomatic, or with HMOD, or CKD stage ≥3, or CVD

Grade 1 Hypertension
BP 140–159/90–99

Grade 2 Hypertension
BP 160–179/100–109

Grade 3 Hypertension
BP ≥180/110

Use HBPM and/or ABPM whenever possible

Diagnosis established – initiate lifestyle interventions

If <150/95
Initiate drug treatment if BP is not controlled

Aim for optimal BP control at least within 3 months

Immediate drug treatment

Diagnosis and Threshold to initiate antihypertensive treatment
### 2023 ESH Guidelines for the management of arterial hypertension

#### Office BP thresholds for drug treatment initiation

<table>
<thead>
<tr>
<th>Recommendations and statements</th>
<th>CoR</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients 18 to 79 years, the recommended office threshold for initiation of drug treatment is 140 mmHg for SBP and/or 90 mmHg for DBP.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients ≥80 years, the recommended office SBP threshold for initiation of drug treatment is 160 mmHg.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>However, in patients ≥80 years a lower SBP threshold in the range 140 – 160 mmHg may be considered.</td>
<td>II</td>
<td>C</td>
</tr>
<tr>
<td>The office SBP and DBP thresholds for initiation of drug treatment in frail patients should be individualized.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In adult patients with a history of CVD, predominantly CAD, drug treatment should be initiated in the high-normal BP range (SBP ≥130 or DBP ≥80 mmHg).</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>
Principle of a BP Treatment Target Range

Target Range below 140mmHg, aiming for 130mmHg is aiming to ensure all BP levels are <140mmHg
Effects of blood pressure (BP) lowering in trials with mean on-treatment systolic BP (SBP) below and above different cut offs.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials (n)</th>
<th>Events (v/patients)</th>
<th>Difference SBP/DIN (mmHg)</th>
<th>Standardized RR (95% CI)</th>
<th>Standardized RR (95% CI)</th>
<th>Absolute Risk Reduction 1000 pts/5 years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>140-149 vs ≥ 150</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>8</td>
<td>265/7284</td>
<td>354/6557</td>
<td>-13.5/-5.1</td>
<td>0.68 (0.60-0.79)</td>
<td>-0.20 (-0.32 to -0.08)</td>
</tr>
<tr>
<td>CHD</td>
<td>8</td>
<td>225/7284</td>
<td>210/6557</td>
<td>-14.0/-5.2</td>
<td>0.68 (0.60-0.79)</td>
<td>-0.20 (-0.32 to -0.08)</td>
</tr>
<tr>
<td>HF</td>
<td>7</td>
<td>116/6221</td>
<td>216/6494</td>
<td>-14.0/-5.2</td>
<td>0.68 (0.60-0.79)</td>
<td>-0.20 (-0.32 to -0.08)</td>
</tr>
<tr>
<td>Stroke + CHD</td>
<td>7</td>
<td>490/7284</td>
<td>554/6557</td>
<td>-13.5/-5.1</td>
<td>0.72 (0.67-0.78)</td>
<td>-0.21 (-0.33 to -0.09)</td>
</tr>
<tr>
<td>Stroke + CHD + HF</td>
<td>7</td>
<td>630/6621</td>
<td>810/6504</td>
<td>-14.5/-5.2</td>
<td>0.68 (0.60-0.76)</td>
<td>-0.21 (-0.33 to -0.09)</td>
</tr>
<tr>
<td>CV Death</td>
<td>8</td>
<td>373/7284</td>
<td>415/6557</td>
<td>-13.5/-5.1</td>
<td>0.76 (0.71-0.89)</td>
<td>-0.21 (-0.33 to -0.09)</td>
</tr>
<tr>
<td>All-cause Death</td>
<td>7</td>
<td>744/7284</td>
<td>747/6557</td>
<td>-13.5/-5.1</td>
<td>0.89 (0.82-0.96)</td>
<td>-0.20 (-0.32 to -0.08)</td>
</tr>
</tbody>
</table>

Mean SBP/diastolic BP (DBP) achieved on treatment were for SBP
- cut off 150, 143.3/76.4 (active) and 157.1/82.2 (control),
- cut off 140, 137.2/81.1 and 144.3/84.8;
- cut off 130, 126.8/78.7 and 136.8/83.7 mm Hg.
CV disease and all-cause mortality and attained systolic blood pressure

<table>
<thead>
<tr>
<th>Major Cardiovascular Disease</th>
<th>Hazard Ratio (95% CI)</th>
<th>Favors Lower Blood Pressure</th>
<th>Favors Higher Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction to 120-124</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 125-129</td>
<td>0.82 (0.67-0.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>120-124 vs 130-134</strong></td>
<td><strong>0.71 (0.60-0.83)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 135-139</td>
<td>0.68 (0.55-0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 140-144</td>
<td>0.58 (0.48-0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 145-149</td>
<td>0.55 (0.42-0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 150-154</td>
<td>0.46 (0.34-0.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 155-159</td>
<td>0.41 (0.32-0.54)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All-Cause Mortality</th>
<th>Hazard Ratio (95% CI)</th>
<th>Favors Lower Blood Pressure</th>
<th>Favors Higher Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction to 120-124</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 125-129</td>
<td>0.74 (0.57-0.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>120-124 vs 130-134</strong></td>
<td><strong>0.73 (0.58-0.93)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 135-139</td>
<td>0.79 (0.59-1.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 140-144</td>
<td>0.59 (0.45-0.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 145-149</td>
<td>0.71 (0.50-1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 150-154</td>
<td>0.51 (0.36-0.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs 155-159</td>
<td>0.49 (0.34-0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-124 vs ≥160</td>
<td>0.47 (0.32-0.67)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bundy JD et al. JAMA Cardiology 2017; 2:775-781
Hazard ratio for outcomes according to the mean systolic blood pressure during the treatment period,

The diastolic blood pressure values for the groups with systolic blood pressure ≥140, 130–139, and <130 mmHg were 82.8 ± 7.8, 79.9 ± 5.9, and 77.2 ± 6.0 mmHg, respectively.
Hazard ratio for outcomes according to the mean diastolic blood pressure during the treatment period,

The systolic blood pressure values for the groups with a diastolic blood pressure ≥90, 80–89, and <80 mmHg were 154.4 ± 4.5, 141.4 ± 10.6, and 137.8 ± 11.0 mmHg, respectively.
<table>
<thead>
<tr>
<th>Condition</th>
<th>SBP* Risk reduction (%)</th>
<th>DBP* Risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>-21 (-34/-6)</td>
<td>-27 (-41/-7)</td>
</tr>
<tr>
<td>CHD</td>
<td>-16 (-29/+1)</td>
<td>-16 (-29/+1)</td>
</tr>
<tr>
<td>HF</td>
<td>-19 (-44/+20)</td>
<td>-23 (-43/+5)</td>
</tr>
<tr>
<td>Stroke + CHD + HF</td>
<td>-22 (-31/-11)</td>
<td>-18 (-25/-10)</td>
</tr>
<tr>
<td>CV death</td>
<td>-20 (-36/+2)</td>
<td>-27 (-45/-10)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>-12 (-26/+6)</td>
<td>-22 (-38/-3)</td>
</tr>
</tbody>
</table>

* Mean BP in more and less intensely treated patients: 122.1/72.5 vs 135.0/75.6 mmHg

Thomopoulos et al., J Hypertens 2016; 34: 613
J-curve relationship between achieved mean on-treatment systolic blood pressure (SBP) and the primary outcomes (CV death, myocardial infarction, stroke, and hospitalization for heart failure)

- Optimal range of SBP
- Risk association at optimal SBP?

- Optimal range of DBP

- Reduced organ perfusion
- Relative overdosing of antihypertensive drugs
- Reverse causation (comorbidities, frailty, etc.)

Böhm et al. Lancet 2017; Bohm M et al. Eur Heart J. 2018
## Blood pressure treatment targets

<table>
<thead>
<tr>
<th>Recommendations and statements</th>
<th>CoR</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients 18 to 64 years old</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The goal is to lower office BP to &lt;130/80mmHg</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>Patients 65 to 79 years old</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The primary goal of treatment is to lower BP to &lt;140/80mmHg</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>However, lowering BP to below 130/80mmHg can be considered if treatment is well tolerated.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td><strong>Patients 65 to 79 years old with ISH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The primary goal of treatment is to lower SBP in the 140 to 150 mmHg range.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>However, a reduction of office SBP in the 130 to 139 mmHg range may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.</td>
<td>II</td>
<td>B</td>
</tr>
<tr>
<td><strong>Patients ≥80 years old</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office BP should be lowered to a SBP in the 140 to 150 mmHg range and to a DBP &lt;80 mmHg.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>However, reduction of office SBP between 130 to 139 mmHg may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.</td>
<td>II</td>
<td>B</td>
</tr>
<tr>
<td><strong>Additional safety recommendations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In frail patients, the treatment target for office SBP and DBP should be individualised.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Do not aim to target office SBP below 120 mmHg or DBP below 70 mmHg during drug treatment.</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>However, in patients with low office DBP, i.e. below 70 mmHg, SBP should be still lowered, albeit cautiously, if on-treatment SBP is still well above target values.</td>
<td>II</td>
<td>C</td>
</tr>
<tr>
<td>Reduction of treatment of can be consider in patient aged 80 years or older with a low SBP (&lt; 120 mmHg) or in the presence of severe orthostatic hypotension or a high frailty level</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
2023 ESH Guidelines for the management of arterial hypertension

NEW updates FOR management of hypertensive patients!!!!!!

- Current back bone: ACEI, ARBs, CCB and thiazide diuretics
- Specific compelling indications and contraindications may exist for each class
- Focus on those with proven benefits beyond BP reduction
BEYOND BP CONTROL
PREVENTION OF END-ORGAN COMPLICATIONS
Calcium channel blockers

(e) Calcium Antagonists vs All Other Drug Classes, separately for Dihydropyridines and Non-dihydropyridines

<table>
<thead>
<tr>
<th>Event</th>
<th>DHP 23</th>
<th>N-DHP 4</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1661/49144</td>
<td>2844/66690</td>
<td>0.73 (0.83–0.93)</td>
</tr>
<tr>
<td>CHD</td>
<td>2187/49144</td>
<td>3771/66690</td>
<td>0.73 (0.92–1.10)</td>
</tr>
<tr>
<td>HF</td>
<td>1769/45105</td>
<td>2582/62669</td>
<td>0.78 (1.08–1.33)</td>
</tr>
<tr>
<td>Stroke + CHD</td>
<td>3345/49144</td>
<td>6617/66690</td>
<td>0.73 (0.89–1.02)</td>
</tr>
<tr>
<td>Stroke + CHD + HF</td>
<td>5452/45105</td>
<td>8998/62669</td>
<td>0.78 (0.98–1.13)</td>
</tr>
<tr>
<td>CV Death</td>
<td>1617/44383</td>
<td>3010/62589</td>
<td>0.69 (0.89–0.99)</td>
</tr>
<tr>
<td>All-cause Death</td>
<td>4088/49133</td>
<td>6908/67359</td>
<td>0.74 (0.93–0.99)</td>
</tr>
</tbody>
</table>

Hypertens 2015;33:1321–1341
Hypertens 2015;33:1321–1341

Thiazide and Thiazide-like diuretic

(e) Diuretics vs All Other Drug Classes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events</th>
<th>Diuretics</th>
<th>Controls</th>
<th>Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>21</td>
<td>1294/45827</td>
<td>1478/49858</td>
<td>0.78/0.23</td>
<td>0.96 (0.85–1.08)</td>
<td>0.03</td>
</tr>
<tr>
<td>CHD</td>
<td>21</td>
<td>2156/45827</td>
<td>2366/49858</td>
<td>0.78/0.23</td>
<td>1.03 (0.95–1.13)</td>
<td>0.09</td>
</tr>
<tr>
<td>HF</td>
<td>12</td>
<td>1108/33431</td>
<td>1582/37353</td>
<td>0.80/0.32</td>
<td>0.83 (0.73–0.94)</td>
<td>0.10</td>
</tr>
<tr>
<td>Stroke + CHD</td>
<td>21</td>
<td>3450/45827</td>
<td>3843/49858</td>
<td>0.78/0.23</td>
<td>1.00 (0.93–1.08)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke + CHD + HF</td>
<td>14</td>
<td>4286/38789</td>
<td>5195/42858</td>
<td>0.78/0.18</td>
<td>0.94 (0.88–1.01)</td>
<td>0.02</td>
</tr>
<tr>
<td>CV death</td>
<td>17</td>
<td>1577/43614</td>
<td>1750/46594</td>
<td>0.83/0.26</td>
<td>1.01 (0.94–1.08)</td>
<td>0.37</td>
</tr>
<tr>
<td>All-cause death</td>
<td>21</td>
<td>3583/45703</td>
<td>3949/49786</td>
<td>0.43/0.59</td>
<td>1.02 (0.98–1.06)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

ESIM

Ethiopian Society of Internal Medicine
# Beta Blockers?

## (e) Beta-Blockers vs All Other Drug Classes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Event</th>
<th>N1</th>
<th>N2</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>13</td>
<td>1171/40381</td>
<td>953/41445</td>
<td>0.80 (0.29)</td>
<td>1.23 (1.07–1.42)</td>
</tr>
<tr>
<td>CHD</td>
<td>13</td>
<td>1568/40381</td>
<td>1553/41445</td>
<td>0.80 (0.29)</td>
<td>1.01 (0.93–1.11)</td>
</tr>
<tr>
<td>HF</td>
<td>7</td>
<td>539/30259</td>
<td>521/31387</td>
<td>0.82 (0.33)</td>
<td>1.05 (0.93–1.18)</td>
</tr>
<tr>
<td>Stroke + CHD</td>
<td>13</td>
<td>2663/40381</td>
<td>2520/41445</td>
<td>0.80 (0.29)</td>
<td>1.06 (0.98–1.16)</td>
</tr>
<tr>
<td>Stroke + CHD + HF</td>
<td>9</td>
<td>3076/35764</td>
<td>2886/36765</td>
<td>1.23 (0.42)</td>
<td>1.09 (0.99–1.19)</td>
</tr>
<tr>
<td>CV Death</td>
<td>12</td>
<td>1322/39608</td>
<td>1213/39717</td>
<td>0.85 (0.27)</td>
<td>1.08 (0.95–1.24)</td>
</tr>
<tr>
<td>All-cause Death</td>
<td>15</td>
<td>2775/40750</td>
<td>2653/41974</td>
<td>0.79 (0.27)</td>
<td>1.06 (0.99–1.13)</td>
</tr>
</tbody>
</table>

Aspect of Figure:
- Beta-Blocks better
- Controls better

. J Hypertens 2015;33:1321–1341
24-HOUR ACEi / ARB EFFICACY: TROUGH-TO-PEAK RATIO

**ACEi**
- Perindopril
- Fosinopril
- Lisinopril
- Ramipril
- Benazepril
- Enalapril

**ARBs**
- Telmisartan
- Losartan
- Valsartan
- Olmesartan
- Irbesartan

*Multiple References*
Importance of Trough-to-Peak Ratio > 75%

TPR, trough to peak.

Evidence for All-cause Mortality Benefits for Specific ACEi and ARBs in Hypertension Trials

Note: Only studies evaluated in this meta-analysis are shown here, based on analysis of all-cause mortality for each trial. *Significant for all-cause mortality. HCTZ, hydrochlorothiazide. Adapted from van Vark LC, et al. Eur Heart J 2012;33:2088-97.

Significant for trial primary endpoint

Telmisartan  Losartan  Valsartan  Irbesartan  Candesartan  Perindopril  Lisinopril  Enalapril

Not significant for trial primary endpoint

PRoFESS  RENAAL  NAVIGATOR  IDNT  SCOPE  HIJ-CREATE  HYVET-Pilot  ANBP2

LIFE (+ HCTZ)  KYOTO-Heart  JIKEI-Heart  VALUE

N = 158,998
20 trials
ON-TARGET TRIAL: PRIMARY ENDPOINT: DEATH FROM CARDIOVASCULAR CAUSES, MI, STROKE, OR HOSPITALIZATION FOR HEART FAILURE.

Changes from baseline in hourly means for SBP at 14 weeks

- This was a comparison between a short acting ACEi vs a long-acting ARB

- This study was in CAD patients and not majorly on hypertensive patients
ON-TARGET TRIAL: PRIMARY ENDPOINT: DEATH FROM CARDIOVASCULAR CAUSES, MI, STROKE, OR HOSPITALIZATION FOR HEART FAILURE.

The better BP control of telmisartan vs a short acting ACEi, did no translate to more cardiovascular protection

Highlighting that more factors beyond BP control are at play when it comes to protecting the patients from CV events

Similar risk reduction in Death from cardiovascular causes, MI, stroke, or hospitalization for heart failure
Meta-analysis of Hypertension Studies: ACEi and ARBs Effects on All-cause Mortality

The ARB Paradox: 2006

Summary of meta-analysis results for ACEi and ARBs assessing a range of CV endpoints. CV, cardiovascular; MI, myocardial infarction.

Adapted from Strauss MH, Hall AS. Circulation 2006;114:838-54; and Hall AS, Strauss MH. Heart 2007;93(9):1011-4.
The ARB Paradox: 2017

Angiotensin Receptor Blockers Do Not Reduce Risk of Myocardial Infarction, Cardiovascular Death, or Total Mortality
Further Evidence for the ARB-MI Paradox

<table>
<thead>
<tr>
<th></th>
<th>ACEi vs placebo</th>
<th>ARB vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MI</td>
<td>CV death</td>
</tr>
<tr>
<td>High risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangalore et al²</td>
<td>0.83 (0.78-0.9)</td>
<td>0.83 (0.7-0.99)</td>
</tr>
<tr>
<td>High risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Savarese³</td>
<td>0.81 (0.75-0.88)</td>
<td>0.9 (0.78-1.03)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>NA</td>
<td>0.83 (0.70-0.99)</td>
</tr>
<tr>
<td>Thomopoulos et al⁵</td>
<td>NA</td>
<td>0.87 (0.78-0.98)</td>
</tr>
</tbody>
</table>

Values indicate HR (95% CI). CV, cardiovascular; MI, myocardial infarction; NA, not applicable.

Meta-analysis: ACEi and ARB Effects on Clinical Endpoints

26 trials, N = 108,212

- **Composite outcome:** CV death, MI, and stroke.
- **CV death**, **MI**, and **Stroke**

*Significant reduction compared to placebo; composite outcome: CV mortality, MI, and stroke.

CV, cardiovascular; MI, myocardial infarction; OR, odds ratio

Diuretics in Hypertension Management

SGLT2i, sodium glucose cotransporter 2 inhibitors.
Comparison of HCTZ and Chlorthalidone: A Systematic Review and Network Meta-analysis

Chlorthalidone is superior to HCTZ in preventing cardiovascular events.
Indapamide Is Superior to HCTZ for BP Reduction

Indapamide more potent HCTZ more potent
Summary of the Efficacy of Diuretics in Hypertension Trials

Higher-dose thiazides (+/- K⁺ sparing)
Chlorthalidone
Indapamide
• Good evidence of CV benefits

Low-dose thiazides vs anything
• Inferior (ANBP2, ASCOT, ACCOMPLISH)

Truly low-dose thiazide vs placebo
• No evidence for benefit

CV, cardiovascular; K⁺, potassium.
Expert Opinion of the Steering Committee.
2023 ESH Guidelines for the management of arterial hypertension

• **For BP reduction:**
  ✓ Thiazides demonstrate a dose-response effect
  ✓ The thiazide-like diuretics, chlorthalidone and indapamide, are more potent and have a longer duration of action compared with hydrochlorothiazide, but a greater incidence of side effects has been reported for chlortalidone in some studies.

• **Major benefits** for reducing **CV events** have been achieved with three types of diuretics:
  – High-dose thiazides (+/- K+ sparing)
  – Chlorthalidone
  – Indapamide

While some guidelines recommend thiazide and thiazide-like diuretics equally, others suggest a preference for thiazide-like diuretics.
Beta Blockers?

- RCTs and meta-analyses demonstrate that as compared with placebo, BBs significantly reduce the risk of stroke, HF, and major CV events in hypertensive pts.

- Preferred antihypertensive agents in
  - symptomatic angina
  - Heart rate control
  - Post-myocardial infarction
  - HFrEF, and
  - As an alternative to ACE inhibitors or ARBs in younger hypertensive women planning pregnancy or of child-bearing potential.
Cochrane meta analysis: BBs may be inferior to some, but not all

- Total mortality and CV events: BB < CCB
- Stroke: BB < CCB and RAS blockers
- CHD: BB = CCB, RAS blockers and diuretics

RCTs based on HMOD have also indicated that BBs are somewhat less effective than RAS blockers and CCBs in preventing or regressing LVH, carotid IMT, aortic stiffness, and small artery remodeling.
Vasodilating BB?

Brachial and Central Aortic Systolic Blood Pressure (±95% CI)

Beta-Blockers and BP variability: ASCOT Study
Group distribution (SD and CV) of measures of SBP at baseline and at each follow-up visit in the two treatment groups

Lancet 2010

ESIM
ETHIOPIAN SOCIETY OF INTERNAL MEDICINE
Multiple Antihypertensive Agents Are Needed to Reach BP Goal

- Initial use of different Monotherapies
- Escalate dose of initial Monotherapy
- Monotherapy substitution
- Stepped-care approach i.e. start with one and add another agent
- Target BP of 140/90 in only 35-40%
Advantages of Single Pill Combinations (SPCs)

- SPC therapy is associated with better adherence vs. free combinations\(^1\)
- A regimen featuring initial prescription of SPC leads to better BP control\(^2\)
- Initial combination therapy is associated with ↓ risk of CV events than monotherapy\(^3,4\)

---

Blood pressure reduction from combining drugs from 4 classes can be predicted on the basis of additive effects.

The extra blood pressure reduction from combining drugs from 2 different classes is approximately 5 * greater than doubling the dose of 1 drug.
At Low Doses the Adverse Effects of Most Antihypertensives Approach those of Placebo

Law, M R et al. BMJ 2003;326:1427
Initial and subsequent combination therapy was associated with a significant reduction in the risk of hospitalisation for CV events. The risk of hospitalisation for CV events during a 3-year follow-up in patients on initial combination was less than that of patients on initial monotherapy.
Early Cardiovascular Protection by initial two-drug single pill combination versus monotherapy in hypertension

N = 37,078 monotherapy
N = 7,456 SPC
2,212 CV events at 1 year

The effect of starting treatment with a SPC versus Monotherapy on 1 year risk of CV outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR^* (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CV event</td>
<td>0.85 (0.74–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>0.73 (0.56–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.83 (0.61–1.14)</td>
<td>0.26</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.90 (0.54–1.51)</td>
<td>0.69</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.63 (0.42–0.94)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

High dimensional propensity score matched in 2212 patients with events at 1 year

Rea F. et al. Eur Heart J. 2018
Choice of Combinations

- Superior combinations

**Combinations Tested or Widely Used in Outcome (CV-renal events) Trials**

- **ACEI / D**
  - PROGRESS
  - ADVANCE
  - HYVET

- **ARB / D**
  - LIFE
  - SCOPE
  - RENAAL

- **ACEI / CA**
  - Syst-Eur
  - Syst-China
  - INVEST
  - ASCOT
  - HOT
  - ACCOMPLISH

- **CA / BB**
  - HOT (2nd used)

- **ARB / CA**
  - RENAAL (with D as well)

- **CA / D**
  - FEVER
  - ELSA
  - VALUE
Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination. Combinations vs. placebo or monotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparator</th>
<th>Type of patients</th>
<th>SBP diff (mmHg)</th>
<th>Outcomes (change in relative risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitor and diuretic combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROGRESS</td>
<td>Placebo</td>
<td>Previous stroke or TIA</td>
<td>-9</td>
<td>-28% strokes ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Placebo</td>
<td>Diabetes</td>
<td>-5.6</td>
<td>-9% micro/macrovasc. events ($P = 0.04$)</td>
</tr>
<tr>
<td>HYVET</td>
<td>Placebo</td>
<td>Hypertensive; ≥ 80 years</td>
<td>-15</td>
<td>-34% CV events ($P &lt; 0.001$)</td>
</tr>
<tr>
<td><strong>ARB and diuretic combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCOPE</td>
<td>Diuretic + placebo</td>
<td>Hypertensive; ≥ 70 years</td>
<td>-3.2</td>
<td>-28% non-fatal strokes ($P = 0.04$)</td>
</tr>
<tr>
<td><strong>Calcium channel blocker and diuretic combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEVER</td>
<td>Diuretic + placebo</td>
<td>Hypertensive</td>
<td>-4</td>
<td>-27% CV events ($P &lt; 0.001$)</td>
</tr>
<tr>
<td><strong>ACE inhibitor and CCB combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>Placebo</td>
<td>Older with ISH</td>
<td>-10</td>
<td>-31% CV events ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>Syst-China</td>
<td>Placebo</td>
<td>Older with ISH</td>
<td>-9</td>
<td>-37% CV events ($P &lt; 0.004$)</td>
</tr>
<tr>
<td><strong>Beta-blocker and diuretic combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coope and Warrender</td>
<td>Placebo</td>
<td>Older hypertensive</td>
<td>-18</td>
<td>-42% strokes ($P &lt; 0.03$)</td>
</tr>
<tr>
<td>SHEP</td>
<td>Placebo</td>
<td>Older with ISH</td>
<td>-13</td>
<td>-36% strokes ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>STOP-Hypertension</td>
<td>Placebo</td>
<td>Older hypertensive</td>
<td>-23</td>
<td>-40% CV events ($P = 0.003$)</td>
</tr>
<tr>
<td>STOP-Hypertension 2</td>
<td>ACEI or conv. antiHT</td>
<td>Hypertensive</td>
<td>0</td>
<td>NS difference in CV events</td>
</tr>
<tr>
<td><strong>Combination of two RAS blockers/ACE inhibitor + ARB or RAS blocker + renin inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ONTARGET</td>
<td>ACE inhibitor or ARB</td>
<td>High-risk patients</td>
<td>More renal events</td>
<td></td>
</tr>
<tr>
<td>ALTITUDE</td>
<td>ACE inhibitor or ARB</td>
<td>High-risk diabetic patients</td>
<td>More renal events</td>
<td></td>
</tr>
</tbody>
</table>
Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparator</th>
<th>Type of patients</th>
<th>SBP diff (mmHg)</th>
<th>Outcomes (change in relative risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor and diuretic combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPPP</td>
<td>BB + diuretic</td>
<td>Hypertensive</td>
<td>+3</td>
<td>+5% CV events (NS)</td>
</tr>
<tr>
<td>ACCOMPLISH</td>
<td>ACE inhibitor + CCB</td>
<td>Hypertensive with risk factors</td>
<td>+1</td>
<td>+21% CV events ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>ARB and diuretic combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIFE</td>
<td>BB + diuretic</td>
<td>Hypertensive with LVH</td>
<td>−1</td>
<td>−26% stroke ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>Calcium channel blocker and diuretic combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELSA</td>
<td>BB + diuretic</td>
<td>Hypertensive</td>
<td>0</td>
<td>NS difference in CV events</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>BB + diuretic</td>
<td>Hypertensive with risk factors</td>
<td>0</td>
<td>NS difference in CV events</td>
</tr>
<tr>
<td>VALUE</td>
<td>ARB + diuretic</td>
<td>High-risk hypertensive</td>
<td>−2.2</td>
<td>−3% CV events ($P = NS$)</td>
</tr>
<tr>
<td>COPE</td>
<td>CCB + BB</td>
<td>Hypertensive</td>
<td>+0.7</td>
<td>NS difference in CV events or stroke</td>
</tr>
<tr>
<td>ACE inhibitor and CCB combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NORDIL</td>
<td>BB + diuretic</td>
<td>Hypertensive</td>
<td>+3</td>
<td>NS difference in CV events</td>
</tr>
<tr>
<td>INVEST</td>
<td>BB + diuretic</td>
<td>Hypertensive with CAD</td>
<td>0</td>
<td>NS difference in CV events</td>
</tr>
<tr>
<td>ASCOT</td>
<td>BB + diuretic</td>
<td>Hypertensive with risk factors</td>
<td>−3</td>
<td>−16% CV events ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>ACCOMPLISH</td>
<td>ACE inhibitor + diuretic</td>
<td>Hypertensive with risk factors</td>
<td>−1</td>
<td>−21% CV events ($P &lt; 0.001$)</td>
</tr>
</tbody>
</table>
Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination.

**Combinations vs. other combinations**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparator</th>
<th>Type of patients</th>
<th>SBP diff (mmHg)</th>
<th>Outcomes (change in relative risk)</th>
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</thead>
<tbody>
<tr>
<td><strong>Beta-blocker and diuretic combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPPP</td>
<td>ACE inhibitor + diuretic</td>
<td>Hypertensive</td>
<td>-3</td>
<td>-5% CV events (P = NS)</td>
</tr>
<tr>
<td>LIFE</td>
<td>ARB + diuretic</td>
<td>Hypertensive with LVH</td>
<td>+1</td>
<td>+26% stroke (P &lt; 0.001)</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>ACE inhibitor + BB</td>
<td>Hypertensive with risk factors</td>
<td>-2</td>
<td>NS difference in CV events</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>CCB + BB</td>
<td>Hypertensive with risk factors</td>
<td>-1</td>
<td>NS difference in CV events</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>CCB + diuretic</td>
<td>Hypertensive with risk factors</td>
<td>0</td>
<td>NS difference in CV events</td>
</tr>
<tr>
<td>NORDIL</td>
<td>ACE inhibitor + CCB</td>
<td>Hypertensive</td>
<td>-3</td>
<td>NS difference in CV events</td>
</tr>
<tr>
<td>INVEST</td>
<td>ACE inhibitor + CCB</td>
<td>Hypertensive with CAD</td>
<td>0</td>
<td>NS difference in CV events</td>
</tr>
<tr>
<td>ASCOT</td>
<td>ACE inhibitor + CCB</td>
<td>Hypertensive with risk factors</td>
<td>+3</td>
<td>+16% CV events (P &lt; 0.001)</td>
</tr>
<tr>
<td><strong>Beta-blocker and CCB combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPE</td>
<td>ARB+CCB</td>
<td>Hypertensive</td>
<td>+0.8</td>
<td>NS difference in CV events or stroke</td>
</tr>
<tr>
<td><strong>ARB and CCB combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPE</td>
<td>CCB + diuretic</td>
<td>Hypertensive</td>
<td>-0.7</td>
<td>NS difference in CV events or stroke</td>
</tr>
<tr>
<td>COPE</td>
<td>CCB + BB</td>
<td>Hypertensive</td>
<td>-0.8</td>
<td>NS difference in CV events or stroke</td>
</tr>
<tr>
<td>COLM</td>
<td>ARB + diuretic</td>
<td>Older hypertensive</td>
<td>0</td>
<td>NS difference in CV events</td>
</tr>
</tbody>
</table>
ASCOT-BPLA Trial
Significant Reduction for CV and All-cause Mortality

... despite similar BP reductions

- Design: 19,257 patients with hypertension + 3 cardiovascular risk factors included in an international, multicenter, prospective, randomized open-blinded trial for an average of 5.5 years*

**Benefits beyond BP control**

CV, cardiovascular.
ACCOMPLISH Trial: Time to First Primary Composite End Point [cardiovascular event and death from CV causes]

11,506 patients

Relative risk reduction of 19.6%  P<0.001

...... despite similar BP reductions
AFRICAN PATIENTS

1. “An RCT with African patients from seven SSA countries has also shown an effective BP reduction (ABPM) using a CCB in combination with either a Thiazide or an ACEi”

2. “This limited evidence suggests that in hypertensive adults of African ancestry, antihypertensive treatment should be largely based on CCBs but also that CCB plus ACEi and CCB plus diuretic combinations can both effectively lower BP, with some suggestion of a greater CV protection by the former combination”

To compare the efficacy of three “free” combinations of two anti-hypertensive agents: starting doses for 2 months: full doses for a further 4 months

24 hour ASBP
Combinations of More than Two Drugs

Real world data on triple combination [Perindopril/Indapamide/Amlodipine]

Trials: PIANIST, PAINT, PETRA

– Better compliance rate
– Better BP control rate (OBP; ABPM)
– Limited incidence of adverse events
– Improvement in metabolic parameters (lipid, glucose)

No less than 30% of the patients need more than two antihypertensive drugs to achieve an effective BP reduction
**RESULTS**

✓ In patients taking a CCB at baseline (n=3,427), addition of perindopril 4 mg/indapamide 1.25 mg reduced the RR of **total death by 28%** (HR 0.72; 95% CI 0.57–0.90; p=0.02) vs. placebo.

✓ The RR reduction for **major CV events** was **12%** (95% CI -10% to 19%) for those taking CCB at baseline.

**ADVANCE – CCB**

<table>
<thead>
<tr>
<th>Event</th>
<th>Active</th>
<th>Placebo</th>
<th>Favours</th>
<th>Risk reduction (95% CI)</th>
<th>P homog</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No baseline CCB</td>
<td>134 (0.8%)</td>
<td>152 (0.9%)</td>
<td><img src="image" alt="Active vs Placebo" /></td>
<td><img src="image" alt="Risk reduction" /></td>
<td><img src="image" alt="P homog" /></td>
</tr>
<tr>
<td>Baseline CCB</td>
<td>77 (1.1%)</td>
<td>105 (1.4%)</td>
<td><img src="image" alt="Active vs Placebo" /></td>
<td><img src="image" alt="Risk reduction" /></td>
<td><img src="image" alt="P homog" /></td>
</tr>
<tr>
<td>TOTAL</td>
<td>211 (0.9%)</td>
<td>257 (1.1%)</td>
<td><img src="image" alt="Active vs Placebo" /></td>
<td><img src="image" alt="Risk reduction" /></td>
<td><img src="image" alt="P homog" /></td>
</tr>
<tr>
<td>Total death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No baseline CCB</td>
<td>283 (1.7%)</td>
<td>250 (1.8%)</td>
<td><img src="image" alt="Active vs Placebo" /></td>
<td><img src="image" alt="Risk reduction" /></td>
<td><img src="image" alt="P homog" /></td>
</tr>
<tr>
<td>Baseline CCB</td>
<td>125 (1.7%)</td>
<td>161 (2.4%)</td>
<td><img src="image" alt="Active vs Placebo" /></td>
<td><img src="image" alt="Risk reduction" /></td>
<td><img src="image" alt="P homog" /></td>
</tr>
<tr>
<td>TOTAL</td>
<td>408 (1.7%)</td>
<td>471 (2.0%)</td>
<td><img src="image" alt="Active vs Placebo" /></td>
<td><img src="image" alt="Risk reduction" /></td>
<td><img src="image" alt="P homog" /></td>
</tr>
</tbody>
</table>
2023 ESH Guidelines for the management of arterial hypertension

NEW updates FOR management of hypertensive patients!!!!!!

Start with Dual Combination Therapy in most patients

- **ACEi or ARB + CCB or T/L Diuretic**
  - Increase to full-dose if well tolerated
  - up to ~ 60% controlled

Start with Monotherapy only in selected patients:
- Low risk hypertension and BP <150/95 mmHg
- or high-normal BP and very high CV risk
- or frail patients and/or advanced age

BB
- Can be used as monotherapy or at any step of combination therapy

ACEi or ARB + CCB + T/L Diuretic
- Increase to full-dose if well tolerated
- up to ~ 90% controlled

True resistant Hypertension
- up to ~ 5%

Consider to consult hypertension specialist in patients who are still not controlled
2023 ESH Guidelines for the management of arterial hypertension

NEW updates FOR management of hypertensive patients!!!!!
2023 ESH Guidelines for the management of arterial hypertension

NEW updates FOR management of hypertensive patients!!!!!

Hypertension in CKD: what do the latest ESH #guidelines recommend?

- **Target** <140/90 in all, <130/80 in most
- ACEi or ARB if uACR>30
- SGLT2i if eGFR>20
- Finerenone in DM if uACR>30, eGFR>25, K<5
- Chlorthalidone as an option in CKD 4-5 with resistant HTN

### CKD stage 1 to 3

eGFR ≥30 ml/min/1.73 m²

- ACEi or ARB + CCB or \( \beta \)Diuretic
  - Increase to full-dose if well tolerated

- ACEi or ARB + CCB + \( \beta \)Diuretic
  - Increase to full-dose if well tolerated

- True Resistant Hypertension
  - Add
    - I) Spironolactone (preferred)
    - or other MRA
    - or II) BB or Alpha-1 Blocker
    - or III) Centrally acting agent

### CKD stage 4 and 5 (not on dialysis)
eGFR <30 ml/min/1.73 m²

- ACEi or ARB + CCB or Loop Diuretic
  - Increase to full-dose if well tolerated

- ACEi or ARB + CCB + Loop Diuretic
  - Increase to full-dose if well tolerated

- True Resistant Hypertension
  - Add
    - I) Chlorthalidone (preferred) or other \( \beta \)Diuretic to Loop Diuretic
    - or II) BB or Alpha-1 Blocker
    - or III) Centrally acting agent

+ SGLT2i or Finerenone
Follow up of patients

Monthly (at least once in 2 months) until control, can be influenced by:

- Severity of hypertension, urgency to achieve BP control, comorbidities
- Once controlled: Individualized
Summary and take home message

• Initiate therapy based on patient’s absolute risk and BP level

• Set BP target in a shared decision making process with the pt

• Patient education is key to improve adherence

• Aim achieving target BP in as short time as possible- not more than 3 months
  ✓ Improves patient confidence/Avoids therapeutic inertia

• Use treatments which have Morbi-mortality data in protecting patients. Use drugs which have EVIDENCE IN THE POPULATION in which it is being used

• Start with combination therapy in most patients
  – Use drugs which are once daily preferable as single pill combinations

• In hypertensive adults of African ancestry, treatment should be largely based on Amlodipine+RAASi & CCB+diuretic combinations for effective BP lowering, with some suggestion of a greater CV protection by the former combination
Thanks for listening
Heart Team TAZMA
Open Heart Surgery Experience

Berhanu H. Mariam, MD
Ass prof of surgery,
Consultant Cardiovascular and thoracic Surgeon
Outline

1. Post MI Acute Mitral Regurgitation

1. Post MI Ventricular Septal rupture and LV apical aneurysm
Surgical Procedures for MI complications

- Ventricular Septal Rupture (VSR)
- Myocardial Rupture
- Left Ventricular Aneurysm
- Acute Mitral regurgitation with papillary rupture
Case 1

- A 62 yrs old male patient was referred from a tertiary center ICU with a 12 hrs history of heaviness in the chest, shortness of breath and profuse sweating.
- He was hemodynamically stable on admission and clinical examination was non revealing.
- Medical history- HTN and Diabetics for the past 7 years on followup,
Case 1…cont’d

- ECG; Sinus rhythm, T-wave inversion in III, aVF and V5-V6
- GDT initiated with NSTEMI impression and kept on cardiac monitoring,
- On 2\textsuperscript{nd} day of admission, he deteriorated with acute shortness of breath and on examination a new pansystolic murmur auscultated.
- Echo: severe MR with Posterior Papillary muscle rupture
- CAG: occluded proximal RCA, unobstructed left system
Case 1...Cont’d
Case 1…Cont’d
Case....Cont’d
Case 2 Discussion

- A 60 yrs old female patient a known HTN on follow up referred with a 3 weeks history of an episode of severe chest pain lasting several hours, with a limiting and progressive dyspnoe on exertion, productive cough of blood tinged sputum
- On admission P/E PR=110 b/m, T=36.4°C, RR=30/min, BP=115/78. Cardiac examination, JVP is raised, auscultation revealed a harsh holosytolic murmur more audible at LLSB with associated thrill,
- Respiratory System auscultation findings include fine crepitation rales all over the lungs field with basal 1/3 bilateral decreased air entry
MI complication...cont’d

• Echocardiography
MI complication...cont’d

• Echocardiography
MI complication...cont’d

• Heart Team TAZMA considered open heart surgery as a best option for the patient and patient taken to Operation Room on 1\textsuperscript{st} July 2023,
MI complication...cont’d
MI complication...cont’d
MI complication...cont’d
MI complication...cont’d
Learning Points

• Ventricular septal rupture (VSR) develops a few days after a transmural MI
• Clinical examination and echocardiography are pivotal in diagnosis of VSR
• Despite high morbidity and mortality rates, Surgical repair remains the gold standard treatment
THANK YOU
8th Annual Internal Medicine Conference and Health Exhibition

Theme: Harmonizing Medical Education with Clinical Services to Improve Healthcare Quality in Ethiopia

Opportunities, Challenges and the way Forward

04-05 August, 2023 | Inter Luxury Hotel Addis Ababa, Ethiopia